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| 09/648,775 | 08/28/2000 | Italo O. Biaggioni | MBHB00-618-A | 7733 |

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| EXAMINER | |
|---|---|
| BERCH, MARK L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/648,775 | BIAGGIONI ET AL. | |
| | Examiner | Art Unit | |
| | Mark L. Berch | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 January 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7,9,10,13-15,23,27 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *7,9,10,13-15,23 and 28* is/are allowed.

6)☒ Claim(s) *27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims. There is no real way of knowing what diseases are and are not covered. $A_{2B}$ receptors are widely distributed and are found in many different cell types, including mast cells (including those in bone marrow), vascular endothelial cells and smooth muscle cells. The $A_{2B}$ receptor is involved in a vast array of body processes, including glycogen synthesis and insulin resistance; bronchodilation; vectorial chloride secretion (from $A_{2B}$ receptors in the basolateral domains of intestinal epithelial cells in the colon); vasodilation; apoptosis of arterial Smooth Muscle Cells; protein synthesis in cardiac fibroblasts; promotion of angiogenesis by a paracrine mechanism; mast cell degranulation; the actions of Adenosine deaminase (ADA); glucose-induced portal vein NO metabolite production; asthma; diabetic retinopathy and retinopathy of prematurity, and cyclic AMP accumulation generally. $A_{2B}$ also stimulates of IL-6 production. This is a pleiotropic cytokine which affects inflammatory reactions, hematopoiesis, bone metabolism, reproduction and aging. It specifically regulates the growth and development of trophoblasts or embryonic stem cells, increases platelet counts, differentiates B cells and is capable of inducing the final maturation of B-cells into immunoglobulin-secreting plasma cells, stimulates the synthesis of ACTH (Corticotropin) in the pituitary, induces the differentiation of mature and immature T-cells into cytotoxic T-cells, helps the body resist Listeria monocytogenes and certain viruses, activates neutrophils, induces the proliferation of thymocytes and probably plays a role in the development of thymic T-cells, induces the synthesis of metallothioneins and increases intracellular zinc levels, and plays a major role in influencing antigen-specific immune responses and inflammatory reactions. IL6 blocks the growth of some solid tumors such as mammary carcinomas, cervical carcinomas,

lung cancer (at least in cell lines), Histiocytic lymphomas, and melanomas, but on the other hand stimulates the growth of others, such as many human myelomas, and cervical tumors. It may also play a role in rheumatoid arthritis, bowel disease, psoriasis, and post-menopausal osteoporosis. $A_{2B}$ also stimulates the production of ERK1/2. ERK1 and ERK2 are widely expressed and are involved in the regulation of meiosis, mitosis, and postmitotic functions in differentiated cells, and thus have a central role in mediating cell migration, division, and survival. ERK1 and ERK2 appear to be involved in stimulating cancers such as malignant melanoma and leukemia. These two kinases are also able to phosphorylate a number of proteins that regulate cytoskeletal proteins, metabolism, chromatin remodeling, and numerous transcription factors (such as Elk1, c-Ets1 and c-Ets2) and other kinases such as $p90^{rsk1}$, MNK1 and MNK2, which in turn have effects of their own. ERK appears to be a critical player in synaptic and neuronal plasticity, and thus plays a role in memory. Stimulation of $A_{2B}$ receptors induces production of IL-8 from HMC-1 cells. IL8 acts to activate neutrophil granulocytes, where it causes the release of enzymes from granules. IL8 also enhances the metabolism of reactive oxygen species and increases chemotaxis and the enhanced expression of adhesion molecules. IL8 actually inhibits histamine release from human basophils induced by histamine-releasing factors , is involved also in mediating pain, and antagonizes IgE production by human B-cells thereby affecting IgM, IgG1, IgG2, IgG3, IgG4, or IgA production. IL8 is chemotactic for all known types of migratory immune cells and inhibits the adhesion of leukocytes to activated endothelial cells. Under some circumstances, IL8 supports angiogenesis. $A_{2B}$ receptors also mediate production of VEGF. VEGF stimulates the proliferation of macrovascular endothelial cells and

significantly influences vascular permeability and is a strong angiogenic protein. It may well be that VEGF released from smooth muscle cells and macrophages may play a role in the development of arteriosclerotic diseases. In endothelial cells VEGF induces the synthesis of von Willebrand factor. It is also a potent chemoattractant for monocytes and thus has procoagulatory activities. In microvascular endothelial cells VEGF induces the synthesis of plasminogen activator and plasminogen activator inhibitor type-1. VEGF also induces the synthesis of the metalloproteinase interstitial collagenase which degrades interstitial collagen type 1, collagen type 2, and collagen type 3 under normal physiological conditions. VEGF plays a role in the development and function of primate follicles and the ovarian corpus luteum.

It should be noted that these four (IL6, IL8, ERK and VEGF) are by no means a complete list, but just some of the more important cytokines and kinases which $A_{2B}$ receptors stimulate the production of. Thus, $A_{2B}$ receptors are involved, both directly and by modulating certain cytokines and kinases, in a complicated and only partially understood array of body processes, some good and some bad. Inevitably, the effects of these four and others will sometimes conflict, so that antagonizing $A_{2B}$ receptors may tend to elevate something by one mechanism and lower it by another. Thus, there is no way of knowing what is actually covered by the claim, but it could be an extremely broad range of diseases.

The list of diseases and disease categories given in the specification is quite extensive. This includes use against Parkinson's disease, dementia, depression, asthma, multiple sclerosis, sepsis, septic shock, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory disease syndrome, TNF-enhanced HIV

replication, TNF inhibition of AZT and DDI activity, organ transplant rejection, cachexia secondary to cancer, HIV, osteoporosis, infertility from endometriosis, cerebral malaria, bronchospastic and allergic diseases as well as other obstructive airway-type bacterial diseases, meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, and adverse effects from GM-CSF treatment, traumatic brain injury, osteoporosis, inflammatory gastrointestinal tract disorders including diarrhea, "cardiac diseases", atherosclerosis, hypertension, vasodilatation, and diseases characterized by abnormal blood vessel growth, such as diabetic retinopathy and cancer, along with providing regulation of smooth muscle tone, cell growth and intestinal function, and modulation of neurosecretion. Note the diversity of this list, and the fact that some of these are broad categories, such as cardiac diseases, cancer, regulation of intestinal function, regulation of cell growth, and dementia, and the fact that it includes some extremely difficult (or untreatable) diseases to treat, such as Parkinson's Disease, ARDS, multiple sclerosis, septic shock and dementia.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 9 is completely generic as to disease; it appears to be the same dose regardless of disease. Also, within categories, there is often no advice as to what is being referred

to. For example, "cancer" appears, but no specific cancers are mentioned. There is mentioned "traumatic brain injury", but no guidance as to which types, as these can be quite varied. There are many different types of dementias.

(4) State of the Prior Art: There has never been a compound which was effective for anything remotely close to the list of disorders listed in the specification.

(5) Working Examples: There are no working examples to any use. The specification establishes binding to the $A_{2B}$ receptor, and no more.

(6) Skill of those in the art: This varies considerably according to what disease is being discussed, and, as noted above, it is unclear which diseases are covered. With regard to some specific diseases listed in the specification:

A. Septic shock is an acute and serious cardiovascular collapse resulting from the systemic response to an overwhelming bacterial infection. It is manifested by hypotension, a reduced response (or none at all) to vasoconstrictors, generalized tissue damage and multi-organ failure, and involves a severe decrease in systemic vascular resistance and maldistribution of blood flow. There are numerous mediators of Septic shock; not only the major pro-inflammatory cytokines IL-1 , IL-6 and α-TNF, but also histamine, complement factor C5a, Beta-endorphin, IL-8, prostaglandin $E_1$, thromboxane B2, platelet activating factor , and oxygen free radicals, all of which have a significant role in the syndrome. All attempts to get an effective treatment of septic shock itself have failed. Of course, massive doses of antibacterials are given to combat the particular strains of bacteria which have caused the septic shock in the first place. Drugs are given to combat the hypotension, and particular problems resulting from the septic shock are themselves treated (e.g. digitalis for heart failure). Thus, while many

types of supportive (adjuvant) care are used, but so far, septic shock itself has no treatment.

B. Dementia is listed, of which Alzheimer's Disease is the most important. The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®) or NMDA antagonist, a property these compounds are not disclosed to have. Other dementias include dementias of the frontal lobe type (DFT) and DFT with motor neuron disease (DFT-MND); more than a dozen dementias collectively called "frontotemporal dementia" (FTD); Shy-Drager Syndrome; Primary progressive aphasia (PPA); Posterior cortical atrophy (PCA); progressive supranuclear palsy; Huntington's Disease; Creutzfeldt-Jakob Disease (CJD), which occurs in both sporadic and familial forms; the Olivopontocerebellar atrophies; Gerstmann-Straussler-Scheinker Disease (GSS); Wernicke–Korsakoff's syndrome; dentatorubro-pallidoluysian atrophy (DRPLA); SCA1, SCA2, SCA3 (Machado-Joseph disease), SCA7, SCA12, SCA17, and possibly other Spinocerebellar Ataxias; cortical-basal ganglionic degeneration (CBDG); Pick's disease; dementia puglistica (DP, or "punch drunk" syndrome); Parkinsonism-dementia complex(PDC); the amyotrophic lateral sclerosis/Parkinsonism-dementia complex(ALS-PDC); Diffuse Lewy Body Disease; and AIDS dementia. Several forms of dementia involve the basal ganglia and their neocortical and subcortical projections and are associated with pyramidal or extrapyramidal movement disorders, such as Parkinson's

disease (PD), Lewy body dementia (LBD), and cortical-basal ganglionic degeneration (CBGD). Vascular dementias include multi-infarct dementia (MID), strategic infarct dementia, LID, ThD, and Binswanger's disease. There are many other dementias.

Many dementias are of totally unknown origin. Some dementias can arise from alcoholism and nutritional impairment, such as Wernicke–Korsakoff's syndrome. Dementias can arise from certain viral illnesses and granulomatous diseases such as syphilis, sarcoid, cryptococcus and Lyme's disease. The AIDS dementia complex (ADC) is an increasingly frequent infectious cause of dementia, arising from HIV. Creutzfeldt–Jakob disease (CJD) is another infectious dementia, arising from prions. Dementias can arise from structural causes, e.g. Chronic communicating hydrocephalus (also called normal pressure hydrocephalus), and brain tumors. Vascular dementias are assumed to arise from stroke. Metabolic, nutritional and endocrine disorders such as Wilson's disease, hepatic cirrhosis, cyanocobalamine (vitamin B12) deficiency, thyroid, parathyroid and adrenal endocrinopathies all have been associated with dementia syndromes. Except for this last category (where the dementia can sometimes be reversed with nutritional therapy or hormone replacement), dementias are almost always untreatable with pharmaceuticals. This shows that the skill level in this art is extremely low relative to the difficulty of the task.

C. Parkinson's Disease is listed in the specification. This presents a situation worse than Alzheimer's Disease. Parkinson's Disease has been highly resistant to pharmaceutical treatment. The disorder is characterized by a deficiency of dopamine. The skill level in this art, relative to difficulty of task, is extremely low. Current drug regimens for

Parkinson's disease are aimed at symptomatic relief, primarily through dopamine replacement therapy, but do not actually treat the disease itself

D. Cancer is listed in claim 33. The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is

because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy. Furthermore, as noted above, IL6 appears to have some chemoprotective role against some types of cancers, e.g. some carcinomas, so that suppressing it would be expected, if anything to make these cancers worse and not better, which is clear evidence that cancers generally cannot be treated.

E. ARDS is the rapid onset of progressive malfunction of the lungs, usually associated with the malfunction of other organs due to the inability to take up oxygen. ARDS is associated with extensive lung inflammation and small blood vessel injury in all affected organs. It has a fatality rate of approximately 40 percent. There is no pharmaceutical treatment. There is only supportive therapy, primarily mechanical ventilators and supplement oxygen.

(7) The quantity of experimentation needed: Especially because of factors 1, 3, 5 and 6, the amount of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For reasons set forth above, the scope of this claim is unknown. It is quite possible that most diseases/disorders/conditions are covered by this claim language.

The declaration is unpersuasive. Declarant states: "6. Those persons working in the area of A2B receptors are aware of mammalian diseases, disorders, and conditions that are mediated by the A2B receptor. The pertinent diseases, disorders, and conditions are described in various textbooks and articles related to Adenosine receptors." However, this presents a conclusion without supporting facts, and as such it is entitled to little or no weight, cf. *In re Etter*, 225 USPQ 1, 6; *In re Grunwell*, 203 USPQ 1055, 1059; *In re Buchner*, 18 USPQ2d 1331; *In re Chilowski*, 134 USPQ 515,521; *In re Brandstadter*, 179 USPQ 286, 293-294, *In re Thompson*, 192 USPQ 275; *Ex parte George* 21 USPQ2nd 1058, 1062.

He has not pointed to any evidence that one of ordinary skill in the art would know which disease are covered and which are not. Declarant has pointed to no list. Most importantly, Declarant has not himself provided anything approaching a list. Instead, he provides 7 papers, and then organizes the teachings of these 7 papers into three broad categories. But that does not constitute a teaching of what the claim would

be understood to cover and not cover. It is a listing of what those 7 papers happened to cover. A different set of 7 papers would have provided a different list.

Additionally, there are significant differences between what the specification has and what appears in these three categories. For example, the specification lists Parkinson's disease, dementia, depression, organ transplant rejection, HIV, osteoporosis, and hypertension, just as examples. None of these fall into the three categories provided. Unless the specification is incorrect, then these three categories as merely some examples. But examples are not enough to establish the clarity of the scope of the claim. As was stated in *Ex Parte Lemoine*, 46 USPQ2d 1432, "A claim is indefinite if it fails to clearly delineate the boundary between the claimed and unclaimed subject matter." See *In re Vogel*, 422 F.2d 438, 442, 164 USPQ 619, 622 (CCPA 1970). ("A claim is a group of words defining only the boundary of the patent monopoly.") See also *In re Vamco Machine & Tool, Inc.*, 752 F.2d 1564, 1577 n.5, 224 USPQ 617, 625 n.5 (Fed. Cir. 1985) (The claim sets forth the metes and bounds of the rights which the applicants seek to obtain). Just providing some examples of categories does not give one a boundary of the claim. If there are many, many types of important diseases, disorders, etc, which are covered by the claim, but are not in the

A second problem is that Declarant is engaging in considerable broadening. For example, the third category is as follows:

*C. Intestinal secretion*

Activation of adenosine $A_{2B}$ receptors present in intestinal epithelial cells stimulates chloride secretion (Strohmeier et al., 1995). This is thought to be the mechanism my which neutrophils induce diarrhea. $A_{2B}$ antagonists, therefore, may be useful in the treatment of diarrhea induced by inflammatory or infectious processes.

But the term "Intestinal secretion" covers much more than chloride secretion, since many more things are secreted in the intestines (e.g. GLP-1, water, oxalate, potassium, etc). Furthermore, that last sentence says, "...by inflammatory or infectious processes." But the actual reference says, in the final sentence, "...secretory diarrhea associated with inflammation." The reference does not refer to diarrhea arising from infection, which is a very important source of diarrhea. Thus, it is not at all clear that one of ordinary skill in the art would consider that diarrhea arising from infection is covered by this claim, yet declarant asserts that it does.

Yet another problem arises from the considerable breadth of the second scope of the second choice:

> *B. Angiogenesis*
> Adenosine $A_{2B}$ receptors are present in endothelial cells, and their activation mediates endothelial cells growth (Grant et al., 1999), an important step for the formation of new blood vessels ("angiogenesis"). $A_{2B}$ antagonists, therefore, may be useful in conditions characterized by abnormal blood vessel growth, as occurs in diabetic retinopathy,

However, Angiogenesis covers not only nearly all forms of cancer other than the leukemias, but some neurodegeneration diseases, respiratory distress in the premature infant, psoriasis and rheumatoid arthritis, diabetic retinopathy, embryonic development, wound repair, atherosclerosis and macular degeneration and many other disorders. For example, in the skin area, this would cover skin diseases with excessive angiogenesis, including Cutaneous malignancies (such as Basal cell carcinoma, squamous cell carcinoma, malignant melanoma and Kaposi's sarcoma), benign vascular tumors (e.g. Hemangiomas), Actinic Keratosis, Psoriasis, and Rosacea. It also appears in rheumatoid arthritis. Further, that wording of "abnormal blood vessel growth" actually covers situations where there isn't enough angiogenisis. Since angiogenesis is required

during the proliferative phase of wound healing, it would also cover skin diseases with insufficient angiogenesis, e.g. nonhealing skin ulcers and other delayed wound healings, including diabetic, venous stasis, and pressure ulcers, which are characterized by inadequate wound granulation. Insufficient angiogenesis also occurs in diseases such as systemic sclerosis (scleroderma), certain forms of infertility (especially blastocyst implantation failure and polycystic ovary syndrome), certain ocular diseases, coronary artery disease, and stroke. This goes far, far beyond what appears in the Grant reference. In fact, what the reference says is: "Our findings raise the possibility that selective $A_{2B}$ adenosine receptor antagonists could be used as a novel therapeutic approach to block the inciting events leading to aberrant angiogenesis in proliferative diabetic retinopathy." (page 705). This is quite different from the sweep of "abnormal blood vessel growth". One of ordinary skill in the art would hardly get such scope from this reference. And the examiner must note that while VEGF inhibition seemed promising in 1998 when this paper was written, no actual drug has arisen from this area, and Semaxanib, a VEGF receptor inhibitor, failed in Phase III tests anti-cancer tests.

Indeed, the art is well aware of the limitations of knowledge in this area. As the reference notes, "knowledge of $A_{2B}$ receptors lags behind that of other receptor types."

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

2/2/04